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BRIEF REPORT

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The impact of postbariatric hypoglycaemia on driving performance: A randomized, single-blind, two-period, crossover study in a driving simulator

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Abstract

Postbariatric hypoglycaemia (PBH) is an increasingly recognized complication of bariatric surgery, but its effect on daily functioning remains unclear. In this randomized, single-blind, crossover trial we assessed driving performance in patients with PBH. Ten active drivers with PBH (eight females, age 38.2 ± 14.7 years, body mass index 27.2 ± 4.6 kg/m^2) received 75 g glucose to induce PBH in the late postprandial period and aspartame to leave glycaemia unchanged, on two different occasions. A simulator was driven during 10 minutes before (D0) and 20 (D1), 80 (D2), 125 (D3) and 140 minutes (D4) after the glucose/aspartame ingestion, reflecting the expected blood glucose (BG) increase (D1), decrease (D2) and hypoglycaemia (D3, D4). Seven driving features indicating impaired driving were integrated in a Bayesian hierarchical regression model to assess the difference in driving performance after glucose/aspartame ingestion. Mean ± standard deviation peak and nadir BG after glucose were 182 ± 24 and 47 ± 14 mg/dL, while BG was stable after aspartame (85 ± 4 mg/dL). Despite the lack of a difference in symptom perception, driving performance was significantly impaired after glucose versus aspartame during D4 (posterior probability 98.2%). Our findings suggest that PBH negatively affects driving performance.

KEYWORDS
bariatric surgery, hypoglycaemia

1 | INTRODUCTION

Postbariatric hypoglycaemia (PBH) is an increasingly recognized late metabolic complication of bariatric surgery. Prevalence estimates range widely because of the differing diagnostic criteria used, but may be as high as 30% of patients undergoing Roux-en-Y gastric bypass (RYGB).[1-3] Affected patients present at least 1 year postoperatively with frequent hypoglycaemic episodes after meals, particularly after those with high glycaemic impact.

Despite the high prevalence of PBH cases among the postbariatric surgery population, little is known about the impact of PBH

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on the performance of daily activities. Driving is a daily activity that requires a range of cognitive, psychomotor and other functional abilities. Whilst previous work showed that hypoglycaemia significantly compromises driving performance in people with diabetes,[4] data in patients with PBH are currently lacking. The aim of this study was to assess driving performance in patients with PBH.

2 | RESEARCH DESIGN AND METHODS

2.1 | Study design, population and procedures

This prospective, randomized, single-blind, crossover study was conducted at the University Hospital Bern and included active drivers aged 18 years or older with PBH after RYGB. The diagnosis was based on the documented postprandial hypoglycaemia (interstitial or blood glucose [BG] values <54 mg/dL)[5] at times of symptoms, relieved by BG correction. Exclusion criteria included motion sickness (evaluated using a test drive in the simulator), weight changes of 5% or more within 3 months, historical or current diabetes, haemoglobin less than 11 g/dL, pregnancy or breastfeeding, severe organ dysfunction and medications known to interfere with BG. The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki after local Ethics Committee approval (2020–00400). All participants provided written informed consent prior to study-related procedures. The study was registered on ClinicalTrials.gov (NCT04330196).

After screening, which also included a 20-minute test drive in the driving simulator to familiarize participants with the procedures of the main experiments, participants attended two visits in random order separated by 48 hours or longer. During the 48 hours before each visit, they adhered to a standardized, weight-maintaining diet (identical for both conditions) and refrained from alcohol, caffeine and physical activity. Participants were also fitted with a continuous glucose monitor and were instructed to correct BG values of less than 54 mg/dL. After an overnight fast, they were admitted to the clinical research unit and ingested 75 g of glucose (GLU) or 700 mg of aspartame (ASP) dissolved in 200 mL of water within 5 minutes in an upright sitting position. Participants were blinded to the type of drink and their BG values during the whole experiment. GLU was administered to trigger PBH in the late postprandial period, whereas ASP was used as a control condition, because it has no impact on glycaemia.[6] The dose of ASP was selected to match the sweetness of the 75 g of GLU according to a prestudy dose-finding experiment in five healthy volunteers considering the range of reported sweetness equivalences in the literature.[6,7] An intravenous catheter was inserted in a cubital vein for frequent BG sampling using a Biosen C-Line glucose analyser (EKF Diagnostics, Barleben, Germany) and GLU administration in cases of severe hypoglycaemia or BG less than 27 mg/dL irrespective of symptoms.

During the visits, participants performed 10-minute drives in a simulator (Carnetsoft BV, Groningen, The Netherlands) before (D0) and at 20 (D1), 80 (D2), 125 (D3) and 140 minutes (D4) after GLU/ASP intake. The time points were selected based on the expected glycaemic trajectory in PBH[3]: BG increase (D1), decrease (D2) and hypoglycaemia (D3 and D4). The simulator scenarios during the different driving phases resembled the same rural environment, but each had a shifted starting point. The order of scenarios was randomly generated and kept identical for both conditions.

We assessed cognitive function using the Digit Symbol Substitution Test (DSST)[8] 135 minutes after GLU/ASP, and symptom perception using the Edinburgh Hypoglycemia Symptom Scale[9] 10, 40, 100, 135 and 150 minutes after GLU/ASP (Figure **S1**).

2.2 | Endpoints and study analysis

The primary endpoint was the difference in driving performance between GLU and ASP across seven driving features that were computed over the glycaemic trajectory: speed and safety margin violation (reflecting traffic rule violations), longitudinal and lateral acceleration, steering wheel, braking pedal and gas pedal acceleration (indicating unsteady and nervous behaviour). The difference in z-score between GLU and ASP for each patient (p), driving phase (d) and feature (f) was calculated with a Bayesian hierarchical regression model as follows:

$$GLU_{f,d,p}^{Driving} - ASP_{f,d,p}^{Driving} = \alpha_p + O + D + D_f,$$

where α_p accounts for subject-specific variation, O for the visit order, D for the pooled fixed-effect across all features, and D_f for the feature-specific random effect (for further details, see Appendix S1). An analogous Bayesian approach (accounting for subject-specific variation and visit order) was used to analyse cognitive performance and symptom perception. Further endpoints were mean, peak and nadir BG as well as cognitive performance and symptom perception.

Because of the lack of pre-existing literature on the primary endpoint, a formal sample size calculation was not applicable. The study was of an exploratory nature, aiming to recruit up to 13 participants, with at least 10 participants completing the study (dropout rate 20%).

TABLE 1 Baseline characteristics

	Number of subjects = 10
Age (y)	38.2 ± 14.7
Sex (f, m)[a]	8 f, 2 m
Body weight (kg)	76.4 ± 10.3
Current BMI[b] (kg/m^2)	27.2 ± 4.6
BMI presurgery (kg/m^2)	42.0 ± 2.4
Total weight loss (%)	−35.0 ± 10.9
Years since Roux-en-Y gastric bypass surgery	5.1 ± 2.5
HbA1c (%, mmol/mol)	5.2 ± 0.3, 33 ± 4
Driving experience (y)	17.4 ± 14.8
Km driven per year	13 150 ± 8538

Note: Data are presented as mean ± standard deviation.
[a]f, female; m, male.
[b]BMI, body mass index.

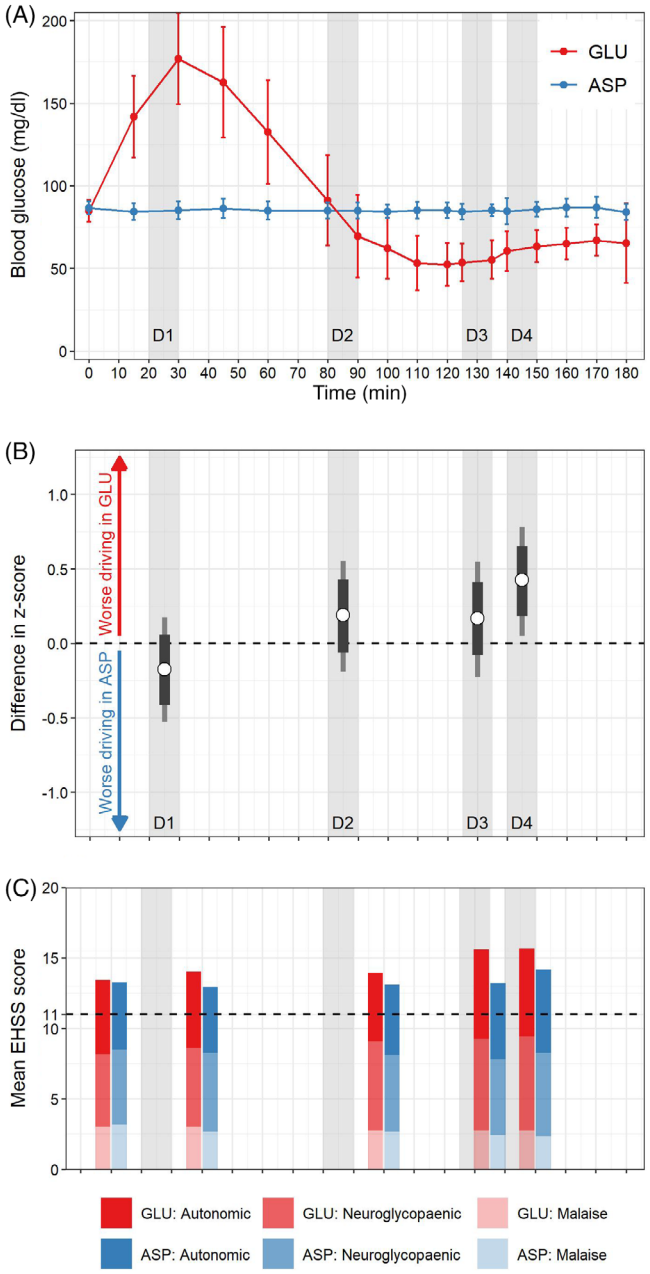

FIGURE 1 (A) Mean blood glucose (mg/dL) over time after glucose (GLU) and aspartame (ASP). The whiskers display the standard deviation. (B) Estimated difference in driving features between GLU and ASP for each driving phase (shaded in grey). Positive difference in z-score indicates deteriorated driving performance in GLU compared with ASP. The black and grey bars display the 80% and 95% credible intervals. (C) Mean perceived total, autonomic, neuroglycopaenic and malaise symptoms during GLU and ASP visits assessed with the Edinburgh Hypoglycemia Symptom Scale (EHSS). The range for the total EHSS score is 11–77. The range for the autonomic, neuroglycopaenic and malaise EHSS score is 4–28, 5–35 and 2–14, respectively. D1 – D4, driving phases 1–4

All statistical analyses were performed with the statistical software R (version 4.0.2). Endpoints are presented as the posterior mean (95% credible interval [CI]) and posterior probability of the z-score difference or mean ± standard deviation. Statistical significance was considered as CI excluding 0.

3 | RESULTS

From July to December 2020, 17 individuals were invited for screening, of whom 12 were randomized (five individuals were excluded as a result of motion sickness) and 10 had complete data and were included in the final analysis (Figure S2). Participants (8/10 females) were aged 38.2 ± 14.7 years, operated on 5.1 ± 2.5 years earlier, and showed a total weight loss of 35.0% ± 10.9%. Additional baseline characteristics are shown in Table 1.

Peak and nadir BG after GLU were 182 ± 24 and 47 ± 14 mg/dL at 32 ± 13 and 121 ± 14 minutes (Figure 1A). Nadir BG was more than 54 mg/dL in two participants (60 and 75 mg/dL, respectively), whilst one participant required intravenous GLU because of BG of 25 mg/dL. After GLU, BG before D1, D2, D3 and D4 was 142 ± 25, 91 ± 27, 54 ± 11 and 60 ± 12 mg/dL, respectively (Figure S3). BG remained stable after ASP (85 ± 4 mg/dL; Figure S4).

Baseline BG (88 ± 6 vs. 87 ± 5 mg/dL) and driving performance during D0 (−0.08 [−0.58, 0.49]) were comparable between GLU and ASP. Whilst no statistically significant differences between the conditions were found during D1, D2 and D3, GLU significantly reduced driving performance during D4 (0.42 [0.03, 0.80]; Figure 1B) compared with ASP. Accordingly, the posterior probability for impaired driving after GLU versus ASP was 15.5% for D1, 84.7% for D2, 84.8% for D3 and 98.2% for D4. Differences in each driving feature for D1–D4 between GLU and ASP are shown in Figure S5.

The DSST performance was significantly lower after GLU versus ASP (−12.5 pairs [−23.90, −1.73]), corresponding to a posterior probability of 99%. Symptom perception was similar between GLU and ASP throughout the experiment and participants reported only a few autonomic and neuroglycopaenic symptoms (Figure 1C and Table **S1**). No adverse events occurred.

4 | DISCUSSION

This study explored the impact of blinded postprandial hypoglycaemia versus euglycaemia induced by ingesting GLU versus ASP on driving performance in patients with confirmed PBH. Impaired driving performance was observed in the late postprandial period, 140 minutes after GLU and was preceded by a lower cognitive test score at 135 minutes. Conversely, symptom perception did not differ between GLU and ASP.

Unlike in people with diabetes in whom the negative effects of hypoglycaemia on several aspects of daily life,[10] including driving performance,[4] are well established, less is known about the implications of PBH. In fact, the high prevalence of asymptomatic PBH[11] has caused uncertainty and scepticism regarding the relevance of this condition. Compared with hypoglycaemia in diabetes, PBH is characterized by a distinct postprandial BG pattern, with a fast BG increase to peak values within 30 minutes and rapid decrease to hypoglycaemia 90–140 minutes postprandially.[3] Although recent work suggests that BG dynamics may be of particular relevance in PBH,[12] driving performance did not differ between GLU and ASP in phases of increasing and decreasing BG. Conversely, impaired driving performance, as

reflected by traffic rule violations and unsteady and nervous driving, was observed with low BG levels, especially if prolonged. This was further supported by a lower cognitive score suggesting that neuromotor skills deteriorate with prolonged hypoglycaemia, even if BG recovered from nadir. Similarly, impaired neuromotor function in adults with type 1 diabetes in a hypoglycaemic clamp study persisted for up to 10 minutes after restoration of euglycaemia.[13]

Worryingly, we found no significant difference in reported hypoglycaemic symptoms after GLU compared with ASP, which is in line with previous studies supporting a high prevalence of asymptomatic PBH patients.[11] The paucity of symptoms may indicate worrying hypoglycaemia unawareness as a result of repeated hypoglycaemia.[14] This may impede corrective self-treatment of hypoglycaemia, which corroborates the need for detection and warning approaches in this population.

The strengths of this study are the novelty of the research question addressing the impact of PBH on driving performance, the standardized design and the inclusion of PBH cases who were blinded to both the provocative stimulus and their glycaemia. We acknowledge the small sample size and the unclear transferability of findings from a simulator to driving risks in real-life conditions. Further studies employing larger sample sizes as well as non-affected surgical and non-surgical controls are warranted to assess the consequences (e.g. accidents) of impaired driving during PBH, and to also contrast the impact of PBH on driving with the effect of other compromised health states (e.g. intoxication, sleep deprivation). Although the driving scenarios exclusively reflected rural environments, this choice was based on their balanced combination of various discriminative driving elements, such as intersections, traffic lights and curves, as well as straight lines. Of note, the nadir BG of two participants during the test was more than 54 mg/dL, despite documented prestudy values of less than 54 mg/dL. This inconsistency could be attributable to a psychological stress-related increase in glycaemia, in line with previous reports.[15] Glycaemia was not standardized using clamp procedures, however, our design allowed replicating the natural course of PBH including gut stimulation, which is critically involved in its underlying pathophysiology.[16]

In conclusion, we report impaired driving performance during PBH alongside a paucity of symptoms. This calls for novel approaches for early PBH detection and prediction, enabling timely preventive or corrective actions.

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CONFLICT OF INTEREST

The authors have nothing to disclose. No competing financial interests exist.

AUTHOR CONTRIBUTIONS

V.L., A.T., D.H. and L.B. designed the study, M.M. set up the driving simulator, J.Z, D.G and P.N contributed to the recruitment of participants, V.L, A.T. and L.B. screened and enrolled participants, V.L., A.T. and J.M. conducted the study visits and collected the data, V.L., A.T., D.H. and M.M. reviewed and prepared the data for analysis, and V.L., A.T., D.H., N.B., S.F., F.W. and L.B. analysed and interpreted the data. V.L., A.T. and L.B. wrote the manuscript, and D.H., J.M., N.B., M.M., J.Z, D.G, P.N, S.F. and F.W. critically reviewed the manuscript. L.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All the authors approved the final draft of the manuscript for submission. V.L. and A.T. should be considered as joint first authors.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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